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EXAMINER				
RAWLINGS, STEPHEN L				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/517,256

Applicant(s)

GRAHAM ET AL.

Examiner

Stephen L. Rawlings

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 January 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 and 6-17 is/are pending in the application.
- 4a) Of the above claim(s) 4 and 11-17 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3 and 6-10 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 December 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)
- Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

1. The amendment filed November 16, 2009, is acknowledged and has been entered. Claim 5 has been canceled. Claims 1, 2, and 6 have been amended.
2. The amendment filed January 21, 2009, is acknowledged and has been entered. Claims 1 and 2 have been amended.
3. Claims 1-4 and 6-17 are pending in the application. Claims 4 and 11-17 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on May 1, 2008.
4. Claims 1-3 and 6-10 are currently under prosecution.

Election/Restrictions

5. As noted in the preceding Office action mailed July 16, 2008, the restriction and election requirement set forth in the Office action mailed April 1, 2008, the inventions of Groups II, III, and IV have been rejoined; and thus to that extent the requirement has been withdrawn.

Priority

6. Applicant's claim under 35 U.S.C. §§ 119(e) and/or 120, 121, or 365(c) for benefit of the earlier filing date of the benefit of PCT Application No. PCT/AU03/00719, filed June 10, 2003, which claims benefit of Australia Patent Application No. PS 2826, filed June 7, 2002, is acknowledged.

However, claims 1-3 and 6-10 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are

rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

In addition, as before noted, claim 3 does not properly benefit from the earlier filing date of Australia Patent Application No. PS 2826 because that document does not describe the claimed invention. Moreover it does not disclose that the prostate cancer cells are androgen independent, nor does it describe experiments that utilized androgen independent prostate cancer cell lines, such as PC3.

Accordingly, the effective filing date of claims 1-3 and 6-10 is deemed the filing date of the instant application, namely January 14, 2005.

Response to Amendment

7. The amendment filed January 16, 2009, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material, which is not supported by the original disclosure, is: the citation of Lash et al. in the paragraph at page 30 beginning in line 29.

Although Applicant has remarked that no new matter has been introduced by the insertion of the amendatory material, it is not evident how, or if the specification, as originally filed, might be considered to provide written support for the added material.

Applicant is required to cancel the new matter in the reply to this Office Action.

Grounds of Objection and Rejection Withdrawn

8. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed July 16, 2008.

Grounds of Objection and Rejection Maintained

Specification

9. The objection to the specification, because the use of improperly demarcated trademarks noted in the application, is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See M.P.E.P. § 608.01(v).

Although Applicant has made a *bona fide* attempt to correct this deficiency, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely Triton™; see, e.g., the paragraph at page 29 beginning in line 30.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at <http://www.uspto.gov/web/menu/search.html>.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. The rejection of claims 1-3 and 6-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is maintained.

Beginning at page 11 of the amendment filed January 16, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 1-3 and 6-10 are indefinite for the following reasons:

The claims use the term "sPLA₂-IIA" as the sole means of identifying the particular polypeptides to which the claims are directed.

As before explained, the use of such terms as the sole means to identify the particular polypeptides to which a claim is directed renders the claim indefinite because different laboratories may use the same laboratory designations to define completely distinct polypeptides.

As further before noted, the same term is often used in the art to describe not one polypeptide, but rather a plurality of polypeptides, which might be structurally and/or functionally related, but otherwise distinct. For example, the same terms are often used to describe various isoforms that are encoded by a single gene, which result from translation of alternatively spliced transcripts of that gene; as another example, the same terms are frequently used to identify polypeptides that occur in different species of animals, which although sharing certain structural and/or functional characteristics have distinct structures and/or functions (e.g., orthologs and paralogs).

In this instance, it is apparent that the same term is used to describe structurally and functionally disparate polypeptides that occur in mouse, rat and human.

Moreover, as noted in the preceding Office action, Markova et al. (*Oncogene*. 2005 Sep 22; 24 (42): 6450-6458) (of record) describes structurally and functionally varying isoforms of "sPLA₂-IIA" occurring in a single species of animal. More particularly, Markova et al. discloses that "sPLA₂-IIA" has been identified as a "tumor modifier", which confers resistance to tumorigenesis by modifying the expressivity or effects of the expression of an oncogene; see entire document (e.g., the abstract; and

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page 6451, column 1). Markova et al. describes variants of "sPLA₂-IIA", which have disparate activities, as having markedly different roles in tumorigenesis; see, e.g., the abstract. For example, Markova et al. describes neoplasia-resistant strains, which were then shown by sequencing to carry variant wild-type alleles of the *Pla2g2a* gene encoding "sPLA₂-IIA"; and in contrast, strains associated with greater numbers of polyps were found to carry mutant alleles (abstract). Accordingly, Markova et al. teaches that the disparate activity levels observed in different strains correlate with differences in the amino acid sequence of the sPLA₂-IIA protein, as well as with the different tendencies of resistant and susceptible strains to develop polyps; see, e.g., page 6456, column 2.

In light of such evidence, it is apparent that the claims do not clearly and particularly identify the "sPLA₂-IIA" polypeptide(s) that are necessarily targeted by the inhibitor, so that inhibition of the activity of the polypeptide(s) results in the inhibition or reduction in the proliferation of prostate cancer cells and/or therapeutic effect.

Therefore, because 35 U.S.C. § 112, second paragraph, requires the claim define the metes and bounds of the subject matter that is regarded as the invention with such clarity and particularity to permit the skilled artisan to know or determine infringing subject matter, and because the term used to describe the polypeptides to which the claims are directed do not unambiguously identify those polypeptides, this requirement has not been met.

It is again suggested that this issue could be remedied by amending the claims to include a recitation of the amino acid sequence of the polypeptides by reference to one or more specific sequence identification numbers of amino acid sequences set forth in the Sequence Listing because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide; but Applicant is cautioned against introducing new matter into the specification by the addition of amendatory material, which is not properly supported by the specification, as originally filed.

However, because the "sPLA₂-IIA" polypeptide(s) to which the claims are directed have more than one function, it may not be sufficient to merely identify the polypeptide(s), but might instead be imperative that the activity that must be inhibited by the inhibitor is identified.

Which one the plurality of activities of "sPLA₂-IIA" must be inhibited in order to inhibit or reduce the proliferation of prostate cancer cells? Which activities must be inhibited by the inhibitor, such that the inhibitor is used to treat prostate cancer in a subject?

In addressing this ground of rejection, Applicant has argued that much of the prior Office action addresses studies describing the role of sPLA₂-IIA in animal models of colon cancer, which are not pertinent to the issues at hand, since the effects described by Markova et al., for example, are tissue and cell line dependent, and the claims are drawn to methods of inhibiting the proliferation of prostate cancer cells.

This argument is not persuasive because the issue at hand is whether or not the use of the term "sPLA₂-IIA" clearly and particularly identifies the polypeptides that must be inhibited by the inhibitor to which the claims are directed, such that the process may be practiced to achieve the claimed objective, namely the inhibition or reduction of the proliferation of prostate cancer cells and/or the treatment of prostate cancer in a subject. As evidenced by the disclosure of Markova et al., for example, the term describes not a single polypeptide, but a plurality of structurally differing polypeptides, which have, at least in the models used by Markova et al., different functions.

It also appears that Applicant has further argued that the use of the term "sPLA₂-IIA" to identify the particular polypeptide that must be inhibited by the inhibitor to which the claims are directed does not render the claims indefinite because claims, as presently amended, are drawn to a method of treating a prostate cancer that is "due to the presence of prostate cancer cells that express sPLA₂-IIA". It is however not evident which cases of prostate cancer are caused by the presence of prostate cancer cells that express "sPLA₂-IIA" because, in part, it is not evident to which polypeptide the term "sPLA₂-IIA" refers.

How might the artisan know or determine if a prostate cancer is caused by the presence of prostate cancer cells that express "sPLA₂-IIA", if the identify of the polypeptide is not known or cannot be determined?

Here is noted that Applicant has argued that it would be clear to one of ordinary skill in the art that the activity that must be inhibited is "the sPLA₂-IIA-mediated proliferation of prostate cancer cells".

While this argument might be persuasive *if the claims were directed to an inhibitor that inhibits the sPLA₂-IIA-mediated proliferation of prostate cancer cells*, none of the claims are clearly and particularly limited such subject matter. The inhibitor to which claim 1, for example, is directed need not inhibit the proliferation of prostate cancer cells; moreover, it need not inhibit "the sPLA₂-IIA-mediated proliferation" of prostate cancer cells. Instead, the inhibitor need only selectively inhibit an unspecified activity of the polypeptide, presumably such that the claimed objective is met by administering the inhibitor to the cells. Not dissimilarly, the inhibitor to which claim 3 is directed need not inhibit the proliferation of prostate cancer cells, but must only inhibit an activity of the polypeptide. As such, Applicant is duly reminded that although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Accordingly, if Applicant regards the invention as a process for inhibiting "the sPLA₂-IIA-mediated proliferation" of prostate cancer cells by administering to the cells (or the subject diagnosed with prostate cancer) an inhibitor of "the sPLA₂-IIA-mediated proliferation", it is suggested the claims be amended to more clearly and particularly claim that subject matter, but still it would not be evident to which polypeptides or which cells and cancers the claims are directed, if the identity of the polypeptides cannot be ascertained. Therefore, because the amino acid sequence of a polypeptide is a unique identifier that unambiguously defines a given polypeptide, Applicant might also amend the claims to include a recitation of the amino acid sequence of the polypeptides by reference to one or more specific sequence identification numbers of amino acid sequences set forth in the Sequence Listing.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

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and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. The rejection of claims 1-3 and 6-10 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Beginning at page 13 of the amendment filed January 16, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The claims are drawn to a method of inhibiting or reducing the proliferation of prostate cancer cells and/or treating prostate cancer in a subject. According to claims 1-3 the process comprises administering to the cells and/or the subject "a selective inhibitor of sPLA₂-IIA"; according to claims 6-8 the inhibitor is a conformationally constrained molecule, such as a cyclic peptide or derivative thereof, which comprises amino acids residues 70-74 of a human "sPLA₂-IIA" polypeptide or their equivalents in other the "sPLA₂" polypeptides; and according to claims 9 and 10, the inhibitor is selected from a finite number of cyclic peptides having a particular formula, including cyclic peptides comprising the amino acid sequences of F-L-S-Y-K, F-L-S-Y-R, and 2NapA-L-S-2NapA-R¹.

Thus, most of the claims, with the notable exception of claim 10, are directed to a genus of substances that are for the most part described only in terms of the objective that must be achieved if those substances are used in accordance with the language of the claims.

Each of the substances encompassed by the claims is a substance that is used to either inhibit or reduce the proliferation of prostate cancer cells that express "sPLA₂-

¹ "2NapA" denotes a non-naturally occurring analogue of alanine, namely 2-naphthylalanine; see paragraph [0026] of the published application.

IIA" or which "treat" prostate cancer in a subject diagnosed with the disease to whom the substance is administered.

According to claims 1-3 the substance is any such substance that selectively inhibits "sPLA₂-IIA"; the substance however need not have any clearly or particularly described structure, just as long as it is capable selecting inhibiting an activity of "sPLA₂-IIA" and can be used to achieve the claimed objectives of the inventions.

Therefore, claims 1-3 are directed to a genus of structurally disparate substances that are solely defined by the effect that each must be capable of causing when administered to prostate cancer cells or a subject diagnosed with prostate cancer.

There is no correlation between any one particularly identifying structural feature and their common functional features that might permit the skilled artisan to immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of substances to which the claims are directed, which must be had in order to practice the claimed inventions to achieve the claimed objectives.

For this reason, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Then, with regard to claim 6, the substance that inhibits "sPLA₂-IIA" is a conformationally constrained molecule, it is a substance (i.e., a molecule) that is *derived* from a peptide; and though the peptide from which the molecule is necessarily derived is a peptide consisting essentially (i.e., comprising) amino acid residues 70-74 of any of a plurality of human "sPLA₂-IIA" proteins or any equivalents thereof, the molecule need not have any particular structure. More particularly, the molecule need not have any particular structure that is correlated to the ability of the molecule to selectively inhibit "sPLA₂-IIA".

This is because a conformationally constrained molecule, per se, does not necessarily have a structure that is correlated with to the ability of the molecule to selectively inhibit "sPLA₂-IIA". In other words, not all conformationally constrained molecules are selective inhibitors of "sPLA₂-IIA" or of any other polypeptide.

This is also because a molecule that is derived from another may not have a structure that even remotely resembles the structure of another molecule from which it is derived.

This is also because the molecule to which the claims are directed is derived from any of a plurality of other molecules, which are not adequately described in this application with any of the requisite clarity or particularity that would be necessary to permit the skilled artisan to immediately envision, recognize or distinguish the molecules.

What residues of other "sPLA₂" proteins should be deemed "equivalents" of amino acid residues 70-74 of any of a plurality of human "sPLA₂-IIA" proteins, and why?

Turning to claim 7, though the molecule that is conformationally constrained is a cyclic molecule, not all conformationally constrained, cyclic molecules, per se, are expected to have the ability to selectively inhibit "sPLA₂-IIA".

Again, though some of the physical features of the molecule are described, its primary structure is not.

Claim 8 is broader than claim 7 in that it encompasses any conformationally constrained, cyclic molecule that selectively inhibit "sPLA₂-IIA" and *derivatives* thereof. The derivative need not have a structure resembling the molecule from which it is derived; moreover, it need not have the same physical features that are used to describe the molecules from which it is derived (i.e., it need not be a conformationally constrained, cyclic molecule).

Only claim 9 is directed to a finite genus of substances that act as selective inhibitors of "sPLA₂-IIA", which are described as having the claimed physical features and a particular structure; but the structure of the molecule may still vary substantially, and it is submitted that the specification would not make apparent that each of the structural variants to which the claim is directed have the ability to selectively inhibit "sPLA₂-IIA" and/or that each can be used to practice the claimed inventions, so as to achieve the claimed objectives.

Then, as explained in prior Office action and in the above rejection of claims, as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it

cannot be ascertained which particular polypeptides are identified by the terms "sPLA₂" and "sPLA₂-IIA", but it is presumed that the claims are directed to any of a plurality of various structural and/or functional variants that are expressed in any of a number of different types of cells and/or tissues in any of a number of different animals.

As before noted, according to Murkami et al. (*J. Biochem.* 2002 Mar; **131** (3): 285-292) (of record), the "PLA₂" family includes at least 19 different enzymes, which catalyze the hydrolysis of the sn-2 position of membrane glycerophospholipids to yield arachidonic acid; see entire document (e.g., the abstract). The *secreted* subfamily of PLA₂ enzymes includes 10 isozymes, which are low molecular weight, calcium cation dependent enzymes that have been implicated in a number of different processes such as modification of eicosanoid generation, inflammation, host defense, and atherosclerosis; see entire document (e.g., the abstract). There is the subfamily of cytosolic PLA₂ enzymes consists of three enzymes, the calcium independent subfamily of PLA₂ enzymes includes two more enzymes, and finally Murkami et al. teaches a subfamily of four members representing a relatively unique group of platelet-activating factor acetylhydrolases (abstract). Despite catalyzing the hydrolysis of the sn-2 position of membrane glycerophospholipids, Murkami et al. describes the family, as a whole, as having rather different structures and biological functions; see, e.g., page 286, Figure 1.

Then, Masuda et al. (*Biochim. Biophys. Acta.* 2005; 1736: 200-210) (of record) discloses that members of the family of PLA₂ enzymes are diversely expressed by cells, even with in the same tissue types and/or organs; see entire document (e.g., the abstract). For example, Masuda et al. teaches in gastric glands exhibiting metaplasia, "sPLA₂-IIA" was localized in the glandular base, "sPLA₂-IID" and "sPLA₂-IIV" were in the glandular body epithelium, "sPLA₂-IIE" and "sPLA₂-IIF" were in goblet cells in the foveolar epithelium, and "sPLA₂-IIX" was in both glandular body epithelial cells and foveolar epithelial goblet cells; see, e.g., the abstract. Masuda et al. teaches that such variations in the cell type-specific expression patterns of different members of the family of PLA₂ enzymes, even within the same tissues, suggest that each has a unique biological role.

Accordingly, claims 6-9 are still rather broadly directed to selective inhibitors of "sPLA₂-IIA", which are conformationally constrained molecules derived from a peptide consisting essentially of amino acid residues 70-74 of a human "sPLA₂-IIA" or the equivalent residues of other any of a very large number of structurally and/or functionally disparate "sPLA₂" polypeptides, and not all of which are expressed in all prostate cells in male animals².

As an example, the previous Office action noted that Suzuki et al. (*J. Biol. Chem.* 2000 Feb 25; **275** (8): 5785-5793) (of record) describes their discovery of a new gene encoding an isoform of the secreted "PLA₂" subfamily that has been designated "sPLA₂-IID", which is only expressed in brain, heart, lung, and placenta, whereas the gene encoding "sPLA₂-IIA" is more broadly expressed; see entire document (e.g., the abstract). Somewhat similarly, Murkami et al. (*supra*) describes "sPLA₂-IIF" as an isozyme having a unique structure, which is expressed only in the testis of mice, but expressed at low levels in a plurality of tissues in humans; see, e.g., page 287, column 2. Then, although claims 5-10 are more narrowly directed to a "sPLA₂-IIA inhibitor", it appears that not even "sPLA₂-IIA" is always expressed by prostate cancer cells. Menschikowski et al. (*Neoplasia*. 2008 Mar; **10** (3): 279-286) describes their recent discovery that while LNCaP and PC-3 prostate cancer cells constitutively express the gene encoding "sPLA₂-IIA", it is not expressed in DU-145 prostate cancer cells; see entire document (e.g., the abstract).

Notably, the absence of expression of the gene encoding "sPLA₂-IIA" in DU-145 prostate cancer cells is apparently due to epigenetic mechanisms. Menschikowski et al. (*supra*) teaches that re-expression of the gene in DU-145 cells was observed following treatment of the cells with 5-aza-2'-deoxycytidine, which suggests that the gene is silenced in those cells by DNA methylation; see, e.g., the abstract.

Logically, if the prostate cancer cell does not express the "PLA₂" or "sPLA₂-IIA", the inhibitor cannot reasonably be expected to inhibit the proliferation of prostate cancer

² Notably the claims do not require the prostate cells to express the polypeptide that is targeted by the claimed "PLA₂ inhibitor"; and in the case of claim 2, the subject need not be human, or even male and/or have a prostate.

cells, either *in vitro* or *in vivo*, or the specification would not reasonably convey to the skilled artisan that Applicant had possession of such an embodiment of the claimed invention at the time the application was filed since it only describes the inhibition of LNCaP and PC-3 cells that express "sPLA₂-IIA" by contacting those cells *in vitro* with two particularly described inhibitors of "sPLA₂-IIA", namely "cFLSYR" and "c(2Nap)LS(2Nap)R"; see, e.g., paragraph [0147]-[0149] of the published application.

Not inconsistently the specification teaches the proliferation of DU-145 prostate cancer cells was not affected by any of the inhibitors (paragraph [0148]; and Figure 4); yet, as indicated, the claims are not limited to prostate cancer cells that express the "PLA₂" that is targeted by the inhibitor, or to prostate cancer cells that are sensitive to the inhibitory effects of the inhibitor.

Applicant has amended claim 1 to recite a limitation that the prostate cancer cells express "sPLA₂-IIA". However, claim 2 does not recite such a limitation, and instead has been amended to recite a limitation that the prostate cancer is "due to the presence of prostate cancer cells that express "sPLA₂-IIA"; yet, the prostate cancer that is treated by the claimed process is not necessarily a prostate cancer that expresses "sPLA₂-IIA". Moreover, it is not immediately apparent what is meant by the limitation now recited in claim 2 since it is not clear how the prostate cancer is "due to" the presence of prostate cancer cells that express "sPLA₂-IIA". Is the expression of "sPLA₂-IIA" the cause of the cancer that is treated, or is the prostate cancer that is treated a prostate cancer that arose from cells expressing "sPLA₂-IIA", but which itself is not necessarily characterized by the expression of the polypeptide(s)?

As also addressed in the preceding Office action and again in the above rejection of claims, as failing to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph, it cannot be ascertained which particular function or activity of the "PLA₂" or "sPLA₂-IIA" is necessarily inhibited by the inhibitor, such that the proliferation of prostate cancer cells is inhibited or reduced and/or the inhibitor is effective to treat prostate cancer in a subject. This issue is particularly important upon consideration of the fact that the inhibitor must *selectively* inhibit "sPLA₂-IIA"; so whatever the activity of "sPLA₂-IIA" that is necessarily inhibited, the molecule must be capable of discriminating the

activity of "sPLA₂-IIA" from the same or similar activities of other proteins in order to preferentially inhibit the activity of the one and not the other.

Then, as also discussed in the preceding Office action and again in the paragraphs above, each member of the family of "PLA₂" enzymes has a unique niche in cellular physiology and different biological functions, if not specific activities, then it follows that the inhibitors to which the claims are directed must have widely varying functions as well, especially if the inhibitors are effective to inhibit the proliferation of prostate cancer cells.

Human sPLA₂-IIA, for example, has the catalytic activity that characterizes all members of the family of phospholipase A₂ ("PLA₂") enzymes, namely the ability to hydrolyze the *sn*-2 position of membrane glycerophospholipids to yield arachidonic acid and free fatty acids, but this enzyme also has other activities, including, for example, the ability to bind to heparin and cell surface associated heparan sulfate proteoglycans (e.g., membrane anchored glypicans), which stimulates an autocrine feedback loop that apparently induces transcription of the gene encoding sPLA₂-IIA, an effect that is independent of the hydrolytic activity of the enzyme³.

Another activity of sPLA₂-IIA, which is apparently independent of its catalytic activity, is its ability to bind to M-type PLA₂ receptor, which transduces signals that lead to such disparate effects in various cell types that include increased expression of COX-2, release of cytokines, and activation of EGFR. sPLA₂-IIA also functions to activate cPLA₂; and in at least colon cancer models, it appears to act as a modifier of the oncogenic effects of APC mutations, actually suppressing polyp formation and ultimately tumorigenesis.

Notably, Finjeman et al. (*Front. Biosci.* 2008 May 1; **13**: 4144-4174) (of record) has very recently reviewed the complexity of sPLA₂-IIA, as its roles have been studied in a number of tissues of different mammals, including mouse and human.

Despite the fact that "sPLA₂-IIA" and other "sPLA₂" enzymes have so many different biological roles, and despite the fact that the claims are broadly directed to an

inhibitor of any of these various different enzymes, the specification fails to describe the actual biological functions and/or specific activities of any of the "sPLA₂-IIA" enzymes to which the claims are directed that must be selectively inhibited by the inhibitors, so as to inhibit the proliferation of prostate cancer cells; and as such, the specification does not describe with the clarity and particularity necessary to satisfy the written description requirement the genus of inhibitors, as a whole, to which the claims are directed.

For example, it has been previously noted that the specification has not described with any clarity or particularity a molecule that selectively inhibits an activity or function of a "sPLA₂-IIA" enzyme encoded by a gene that is expressed in the androgen independent prostate cancer cell line, DU-145, which can be used to practice the claimed invention to achieve the claimed objective of inhibiting or reducing the proliferation of the prostate cancer cell line.

In this regard, it is noteworthy that Rose et al. (*Prostate*. 1991; **18** (3): 243-254) (of record) teaches PC-3 cell growth was inhibited by omega-3 dietary fatty acids present in fish oils, namely docosahexaenoic acid and eicosapentaenoic acid in a dose-dependent manner, but the growth of DU-145 cells, which is also androgen independent, was less sensitive to such treatment; see entire document (e.g., the abstract). In addition to this difference, Rose et al. reports that PC-3 cells are stimulated by linoleic acid, whereas Du-145 cells are not; see, e.g., page 245.

The differences described by Rose et al. (*supra*) between different androgen independent prostate cancer cell lines, together with the disclosure by Menshikowski et al. (*supra*) and the findings reported in the specification, underscore the high level of unpredictability in the art, and add to a bevy of data suggesting that the results of *in vitro* studies must be interpreted cautiously, since those results are not always extrapolated to predict the response of prostate cancer cells *in vivo*⁴.

³ See Jaulmes et al. (*Arterioscler. Thromb. Vasc. Biol.* 2005 Jun; **25** (6): 1161-1167) (of record); entire document (e.g., the abstract; and page 1161, column 2).

⁴ Support for this position is found in the disclosure by Kelland et al. (*Eur. J. Cancer*. 2004 Apr; **40** (6): 827-836) (of record) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). Kelland et al. discusses, despite the limitations of xenograft models, "It is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even *in silico* methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2).

Menschikowski et al. (*supra*) points out an additional difference that was observed between LNCaP cell and PC-3 cells, which should be considered as well. In particular, Menschikowski et al. (*supra*) teaches that the expression of the gene encoding "sPLA₂-IIA" in PC-3 cells is upregulated upon exposure of the cells to γ -interferon (IFN- γ), yet the gene in LNCaP cells is not; see, e.g., the abstract.

Therefore, as explained in the preceding Office action, given the fact that prostate cancer cell lines LNCaP, PC-3, and DU-145 have such different phenotypes, it is submitted that *none can be fairly considered representative of the genus of prostate cancer cells to which the claims are directed, and particularly not those that occur in subject afflicted by the disease.* If so, the disclosure in this application that the cyclic peptides "cFLSYR" and "c(2Nap)LS(2Nap)R") are capable of inhibiting the proliferation of LNCaP and PC-3, but not DU-145 should not be considered reasonably descriptive of the claimed subject matter, as a whole.

Furthermore, although the particularly described inhibitors (i.e., "cFLSYR", "cFLSYK", and "c(2Nap)LS(2Nap)R") have structures similar to an inhibitor of "sPLA₂-IIA" described by the prior art⁵, namely the linear peptide having the amino acid sequence of residues 70-74 of a purified human sPLA₂-IIA enzyme, which consists of SEQ ID NO: 5 (F-L-S-K-Y), the claimed inhibitors need not have any particular structure, and might be composed of any material. The inhibitors are not necessarily peptides in other words, and might instead be small molecules or antibodies, for example.

Given the fact that the inhibitors to which claims 1-3 and 6-8 are directed may have any structure, and may act to inhibit the biological functions and/or specific activities of such a disparate plurality of enzymes, it is apparent that none of the particularly described inhibitors is fairly considered representative of the genus of inhibitors, as a whole. In fact, because the specification does not disclose any particularly identifying structural features that correlate with the ability of such materially

⁵ See, e.g., Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998) (of record); see entire document (e.g., the abstract). Tseng et al. discloses that the "70-74-peptide" (F-L-S-Y-K) forms a non-

and structurally different molecules to inhibit the function or activity of the "sPLA₂-IIA" proteins (and/or "PLA₂" proteins) to which the claims are directed, the skilled artisan could not immediately envision, recognize or distinguish at least a substantial number of the members of the claimed genus of inhibitors.

Accordingly, Applicant is again reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes with the clarity and particularity the genus of structurally disparate substances to which the claims are directed that can be used to inhibit or reduce the proliferation of prostate cancer cells and/or achieve the claimed therapeutic effect in subjects afflicted with prostate cancer. *A description of what a material does, rather than of what it is, does not suffice to describe the claimed invention.*

As before explained, while the written description requirement can be satisfied without an actual reduction to practice, the disclosure of a catalog of potentially effective substances that might be found to be useful in practicing the claimed invention does not fulfill the written description requirement. Recognizing that the claims are drawn to a method comprising administering to prostate cancer cells and/or a subject an unspecified substance having the ability to selectively inhibit an activity of "sPLA₂-IIA", so as to be therapeutically effective, it is aptly noted that the Federal Circuit has decided that a generic statement that defines a genus of substances by *only* their functional activity, i.e., the ability to selectively inhibit an activity of "sPLA₂-IIA", so as to cause a reduction in the proliferation of prostate cancer cells in a subject to whom it administered, does not provide an adequate written description of the genus. See *The Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CAFC 1997). The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by

covalent complex with the amino-terminus of low molecular weight, type II sPLA₂ enzymes to inhibit

reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Although *Lilly* related to claims drawn to genetic material, the statute applies to all types of inventions. "Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). The claimed method depends upon finding a substance that has the ability to selectively inhibit an activity of "sPLA₂-IIA", which can be used to inhibit or reduce the proliferation of prostate cancer cells and/or to achieve therapeutic effect in treating prostate cancer using the claimed process; without such a substance, it is impossible to practice the invention.

As also explained in the preceding Office action, although the skilled artisan could potentially identify substances that might be used in practicing the claimed invention by screening for substances that are capable of inhibiting an activity of "sPLA₂-IIA" and, in turn, the proliferation of prostate cancer cells, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Absent the adequate description of a representative number of members of the genus of the selective inhibitors of "sPLA₂-IIA" to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify a substance that can be used as an agent for treating cancer by inhibition of an activity of "sPLA₂-IIA".

Again, Guidelines states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of substances having the ability to inhibit an activity of "sPLA₂-IIA" and, in turn, the proliferation of prostate cancer cells, so as to be capable of causing a beneficial therapeutic effect in the treatment of prostate cancer in a subject, where these substances otherwise vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

Finally, in light of the disclosure of Menshikowski et al. (*supra*), Rose et al. (*supra*), and Murkami et al. (*supra*), for example, it is apparent that the skilled artisan cannot predict whether the proliferation of prostate cancer cells can be inhibited using the claimed invention because, in part, it cannot be predicted whether the cells express the "sPLA₂-IIA" that is targeted by any given inhibitor, it cannot be predicted whether the proliferation of the cancer cells will be sensitive to inhibition by any given inhibitor, and it cannot be predicted which substances are capable of inhibiting which "sPLA₂-IIA" enzymes in the prostate cancer cells of any of the various different subjects that are encompassed by the claims.

As such, Applicant is once again reminded that the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail below in the preceding Office action and again in the following rejection of claims, as lacking an enabling disclosure, there is in fact a very high level of unpredictability in the art, which is not been assuaged despite recent advancements in the knowledge and skill of the artisan.

As before, it is submitted that, at best, the specification would only reasonably convey Applicant's possession of a method for inhibiting the proliferation of certain human prostate cancer cells, such as PC-3 and LNCaP, which express a human sPLA₂-IIA having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R"), which are analogues of the linear peptide consisting of SEQ ID NO: 5 (F-L-S-K-Y), as described by Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998) (of record).

For all of the above reasons, although Applicant's arguments have been carefully considered, it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

14. The rejection of claims 1-3 and 6-10 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a method for inhibiting the proliferation of certain human prostate cancer cells *in vitro*, such as PC-3 and LNCaP, which express a human sPLA₂-IIA having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R"), **and while being enabling for using** any process that is encompassed by the claims, which is taught by the prior art, **does not reasonably provide enablement for using** the claimed methods for inhibiting or reducing the proliferation of any prostate cancer cells and/or for treating prostate cancer in a subject, said methods comprising administering to the cells or to the subject any selective inhibitor of any "sPLA₂-IIA" enzyme, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Beginning at page 13 of the amendment filed January 16, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

For reasons explained in detail in the preceding Office action it is again submitted that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Here, there is now a preponderance of factual evidence of record that, at best, the specification would only reasonably convey Applicant's possession of a method for inhibiting the proliferation of certain human prostate cancer cells, such as PC-3 and LNCaP, which express a human sPLA₂-IIA having an activity that is inhibited by the particularly described inhibitors "cFLSYR" and "c(2Nap)LS(2Nap)R"), which are analogues of the linear peptide consisting of SEQ ID NO: 5 (F-L-S-K-Y), as described by Tseng et al. (*J. Biol. Chem.* 1996 Sep 27; **271** (39): 23992-23998) (of record).

This conclusion is largely based upon the disclosures in the specification, which show that the cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R" are capable of inhibiting the proliferation of two prostate cancer cell lines, namely LNCaP and PC-3, but incapable of inhibiting another (i.e., DU-145); see, e.g., Figure 4.

In contrast to the breadth of such a showing, the claims are far more broadly drawn to methods for inhibiting or reducing the proliferation of any prostate cancer cells and/or for treating prostate cancer in a subject, which comprise administering to the cells or to the subject any inhibitor of any "PLA2" or "sPLA₂-IIA" enzyme.

Applicant is again reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Thus, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a substance having the ability to inhibit an activity or biological function of a "PLA2" or "sPLA₂-IIA" enzyme, so as to be useful in practicing the claimed invention to achieve the claimed objective of inhibiting or reducing the proliferation of any prostate cancer cells and/or for treating prostate cancer in a subject; yet, defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d 1068, 1071 (BPAI 1991).

The specification describes the rationale that was used to develop the particularly described cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R", which are shown to be capable of inhibiting the proliferation of LNCaP and PC-3 cells *in vitro*. At

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paragraph [0143] of the published application, for example, the specification discloses the following:

We have previously shown that human sPLA₂-IIA is dose-dependently inhibited by a pentapeptide sequence comprising residues 70-74 of the native sPLA₂.sub.2-IIA protein (⁷⁰FLSYK⁷⁴) (Tseng, A., et al., (1996) J. Biol. Chem. 271:23992-23998). Because of the inherent flexibility of the linear peptide sequence, inhibition was weak in in vitro activity assays. We have recently designed two novel cyclic peptides (Church, W. B. et al.), cFLSYR and a cyclic peptide where F and Y are substituted with 2-naphthylalanine (c(2NapA)LS(2NapA)R). Both have shown significant improvement in potency over linear peptides. The potent stimulatory effect of exogenous sPLA₂-IIA on prostate cancer cell number was completely blocked by the sPLA₂-IIA inhibitor, cFLSYR (FIG. 2B) at all concentrations tested.

However, the claims are not limited to these particularly described peptide analogues of the linear peptide first described by Tseng et al; and the specification discloses that the inhibitor can be virtually any substance that is capable of inhibiting a "PLA₂" or "sPLA₂-IIA" enzyme, including, for example, peptides, peptidomimetics, proteins, antibodies, small molecules, and even antisense compounds, catalytic nucleic acids, or RNA inhibitors, which presumably inhibit the activity of a "PLA₂" or "sPLA₂-IIA" enzyme indirectly by inhibiting the expression of the gene or the translation of the gene product; see, e.g., paragraphs [0050]-[0099] of the published application. Additionally, the specification discloses that the inhibitor is not limited to an inhibitor of the "sPLA₂-IIA" expressed by LNCaP and PC-3 prostate cancer cells, but may inhibit any "PLA₂" enzyme, including the type 1B, type IIA, type IID, type IIE, type IIF, type III, type IV, type V, and type X enzymes; see, e.g., paragraph [0013] of the published application.

Given the evident disparity in the breadths of the claims and the amount of guidance, direction and exemplification set forth in the specification, it is apparent that the specification would not have reasonably enabled the skilled artisan to make and then use at least a substantial number of such materially, structurally, and functionally varying inhibitors of such a large number of structurally and functionally varying enzymes, at least not without undue and/or unreasonable experimentation.

Then, even if the artisan were capable of making the various different inhibitors, it could still not be known or predicted which would be effective to inhibit or reduce the

proliferation of any prostate cell, including those of different mammals, and/or to treat prostate cancer in a subject.

Again, while the data presented in the specification demonstrate the inhibition of LNCaP and PC-3 cells that express "sPLA₂-IIA" upon contact with the cyclic peptide inhibitors designated "cFLSYR" and "c(2Nap)LS(2Nap)R", the specification also teaches the proliferation of DU-145 prostate cancer cells was not affected by either one of these inhibitors (paragraph [0148]; and Figure 4).

In fact, the disclosure fails to teach an inhibitor that inhibits an activity or function of a "PLA₂" enzyme encoded by a gene that is expressed in the androgen independent prostate cancer cell line, DU-145; and the amount of guidance, direction, and exemplification that is set forth in this application would not reasonably enable the skilled artisan to make and then use an inhibitor of the activity of a "PLA₂" or "sPLA₂-IIA" enzyme, which is effective to inhibit the proliferation of DU-145 prostate cancer cells.

As discussed in the written description rejection above, the differences described by Rose et al. (*supra*) between different the androgen independent prostate cancer cell lines PC-3 and LNCaP, together with the disclosure by Menshikowski et al. (*supra*) and the findings disclosed in the specification itself, underscore the high level of unpredictability in the art, and add to a bevy of data suggesting that the results of *in vitro* studies must be interpreted cautiously, since those results are not always extrapolated to predict the response of prostate cancer cells *in vivo*.

Kelland et al. (*supra*) has reviewed the reliability of the model in predicting clinical response; see entire document (e.g., the abstract). Kelland et al. discusses, despite the limitations of xenograft models, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even *in silico* methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2).

Here, the only experiments disclosed are experiments that were conducted *in vitro* using three different prostate cancer cells lines: the androgen dependent LNCaP cell line, and the androgen independent cell lines, PC-3 and DU-145. No experiments

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were performed *in vivo* using an appropriate animal model, such as the mouse xenograft.

Nonetheless, as noted, Kelland et al. (*supra*) addresses the limitations of such animal models.

In this regard, Kelland et al. teaches, though the successful use of such models in cytotoxic drug development is conclusive, today, there is far less focus on the development of such drugs (page 833, column 2); rather, the focus is upon the development of "molecularly-targeted", largely cytostatic drugs, such as those disclosed in the instant application, which may act in synergy with other drugs to selectively reduce or inhibit the growth of neoplastic cells (e.g., page 885). In particular, where such drugs are naked humanized antibodies that act through mechanisms such as ADCC, Kelland states the models are of limited value, because such mechanisms depend upon the recruitment of the host's (i.e., mouse) immune response, which differs from or is not reflective of that found in man (page 834, column 2). With such limitations of the xenograft model in mind, Kelland suggests that the case for using the model within a target-driven drug development cascade need to be justified on a case-by-case basis (page 835, column 1).

Gura (*Science*. 1997; **278**: 1041-1042) (of record) has also questioned the wisdom of conventional reliance upon the xenograft model to predict the outcomes of candidate therapies in humans. Gura teaches that although researchers had hoped that xenografts would prove to be better models for studying cancer in humans and screening candidate therapeutic agents for use in treating patients diagnosed with cancer, "the results of xenograft screening turned out to be not much better than those obtained with the original models". Gura states that as a result of their efforts, "[w]e had basically discovered compounds that were good mouse drugs rather than good human drugs".

Dennis (*Nature*. 2006 Aug 7; **442**: 739-741) (of record) echoes these concerns. Dennis reports, despite their present indispensability, mouse models, such as xenografts, have only limited utility in predicting the clinical effectiveness of anticancer treatments; see entire document (e.g., page 739, column 2). Dennis explains there is a

"laundry list" of problems associated with the use of mice to model human diseases, such as cancer (page 739, column 1). Accordingly, Dennis reports, "[a]lthough virtually every successful cancer drug on the market will have undergone xenograft testing, many more that show positive results in mice have had little or no effect on humans, possibly because the human tumours are growing in a foreign environment" (page 740, column 1). Therefore, quoting Howard Fine, Dennis concludes: " 'Mice are valuable but they are, after all, still mice' ", suggesting the best study subject will always be the human (page 741, column 3).

Schuh (*Toxicologic Pathology*. 2004; **32** (Suppl. 1): 53-66) (of record) reviews the trials, tribulations and trends in tumor modeling in mice to disclose, for example, that "[c]ommon reliance on survival and tumor burden data in a single mouse model often skews expectations towards high remission and cure results; a finding seldom duplicated in clinical trials" (abstract). Furthermore, Schuh discloses, "[d]espite historical significance and ongoing utility, tumor models in mice used for preclinical therapeutic intervention often error towards false positive results and curing cancer in mice" (page 62, column 1). Given the noted limitations of xenograft models, Schuh suggests that testing in tumor-bearing animals may help to improve the predictive value of animal modeling; see entire document (e.g., the abstract).

Bibby (*Eur. J. Cancer*. 2004 Apr; **40** (6): 852-857) (of record) teaches that in the interest of finding more clinically relevant models, orthotopic models have been developed; see entire document (e.g., the abstract). In such "orthotopic" models, treatment is initiated after removal of the primary tumor and distant metastases are well established and macroscopic. These models have their advantages, but the procedures involved in using such models are far more difficult and time-consuming than conventional subcutaneous (e.g., xenograft) models; see, e.g., page 855, column 2.

Peterson et al. (*Eur. J. Cancer*. 2004; **40**: 837-844) (of record) teaches numerous agents have show exciting activity in preclinical models and yet have had minimal activity clinically; see, e.g., the abstract. Such disappointments, Peterson et al. discloses, "have led to reasonable skepticism about the true value of both syngeneic and

xenograft rodent tumour models in accurately identifying agents that will have important clinical utility" (abstract). Peterson et al. reviews the limitations of the xenograft models; see entire document (e.g., page 840, column 2).

Finally, Saijo et al. (*Cancer Sci.* 2004 Oct; **95** (10): 772-776) (of record) recently reviewed the reasons for negative phase III trial of molecular-target-based drugs and their combinations; see entire document (e.g., the abstract). Saijo et al. discloses that while numerous phase III trials have been conducted upon the basis of promising preclinical data such as that disclosed in the instant application, few have yielded strongly positive results, and the majority of results have been negative (e.g., abstract). Saijo et al. discloses that there are problems in preclinical prediction of combined effects of anticancer drugs, and the results of preclinical prediction of combined effects have been very poor (page 773, column 2). Saijo et al. teaches many reasons for the poor predictability of combined effects (page 774, Table 6).

Thus, taken collectively, there is a preponderance of factual evidence of record that the showing provided in the supporting disclosure would not have enabled the skilled artisan to practice the claimed invention, so as to achieve the claimed therapeutic objective in treating prostate cancer in subjects – not without undue and/or unreasonable experimentation, as required under the provisions of 35 U.S.C. § 112, first paragraph.

It is recognized that since the filing date sought by Applicant additional *in vivo* experiments have been performed using a xenograft mouse model of prostate cancer in which an immunodeficient nude mouse has been inoculated subcutaneously with PC-3 prostate cancer cells and treated with either one of the two cyclic peptides described in this application as being capable of inhibiting the proliferation of PC-3 cells *in vitro* (i.e., the cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R"). This study is described by Sved et al. (*Cancer Res.* 2004 Oct 1; **64**: 6934-6940) (of record); see entire document (e.g., the abstract).

First of all, it is important to remind Applicant that supporting documents of the sort cannot be relied upon to correct the deficiencies of the specification by supplying

the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a).

Nevertheless, it is submitted that the results of the study described by Sved et al. (*supra*) fail to establish that the claimed invention can be used to inhibit or reduce the proliferation of any prostate cancer cell, either *in vitro* or *in vivo*, and/or to treat prostate cancer in a subject, such a human patient known to be afflicted by the disease.

In part, this is because, as explained in the preceding paragraphs, even encouraging preclinical studies in xenograft animal models have often failed to correctly predict the outcome of using the same therapeutic agents to treat the same disease in humans. As noted there are many reasons that the results of such studies poorly extrapolate to accurately infer or predict the effectiveness of candidate therapeutic agents and regimens in humans, but as an example, the results seen in the models are the effects of treating human tumors growing in the foreign environment of immunodeficient mice, which is a biological system that does not sufficiently mirror the variations and complexities of the clinical situation in the population of human patients.

In addition, it is noted that Sved et al. (*supra*) teaches that the cyclic peptide designated "cFLSYR" had no effect upon tumor burden in the mice when administered in a dose of 1 mg/kg; see, e.g., page 6939, column 1. Sved et al. teaches that only the cyclic peptide designated "c(2Nap)LS(2Nap)R" had any effect in the mice, when administered at this same dose, slowing the rate of growth of PC-3 tumors, as compared with the rate of growth observed in control mice that were not treated with the peptide (page 6939, column 1). The other peptide (i.e., "cFLSYR") was only effective when administered at a substantially larger dose of 10 mg/kg; see, e.g., page 6939, Figure 7.

Then, as described in the specification, Sved et al. (*supra*) also teaches the proliferation of LNCaP and PC-3 cells was inhibited the cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R", but the proliferation of DU-145 prostate cancer cells was not; see, e.g., page 9639, Figure 6.

Such variable sensitivity and other phenotypic differences between prostate cancer cell lines suggest that their use should not be relied upon in preclinical studies

designed to ascertain whether the claimed invention might be used to achieve the claimed therapeutic effect in treating subjects afflicted by prostate cancer using the claimed inhibitors. Again, Kelland (*supra*) notes, at present, "it is premature and too much a 'leap of faith' to jump directly from *in vitro* activity testing (or even *in silico* methods) to Phase I clinical trials (via preclinical regulatory toxicology)" (page 835, column 2). Accordingly, despite the evident limitations of the xenograft models, Kelland et al. does not altogether discount the usefulness of such models. Kelland, however, does not advocate the use of a single xenograft model to exhort one to accept assertions of the effectiveness of treating prostate cancer, in general, using the same agent, as has been done in the instant application, since Kelland compels one to decide on a case-by-case basis whether such a model is suitable or not. Here, it is not known if the PC-3 xenograft model used, or the DU-145 xenograft model not used, might serve as the better model; so despite the encouraging results reported by Sved et al., any inferences based upon the results of a relatively limited analysis as to how effective the cyclic peptides described therein will be in treating prostate cancer in humans should be carefully deliberated.

In this regard, Menschikowski et al. (*supra*) discloses both PC-3 and DU-145 prostate cancer cells are highly aggressive, whereas LNCaP cells are not (page 284, column 1). The metastatic potentials of these different cells correlates with the expression of proangiogenic genes; and based on these properties, Menschikowski et al. (*supra*) discloses that the expression profiles of sPLA₂ isoforms suggest that sPLA₂-IIA plays only a secondary role, if any in tumorigenicity (page 284, paragraph bridging columns). As such, Menschikowski et al. (*supra*) suggests that additional studies are needed to elucidate the contributions of various sPLA₂ isoforms to proliferation, migration, invasion, cell-to-cell interaction, and other activities in prostate cancer cells (page 284, column 2).

In addition, Menschikowski et al. (*supra*) notes that although sPLA₂-IIA is not expressed in DU-145 cells, other sPLA₂ isoforms, such as sPLA₂-IIV might compensate for the loss in expression of the gene encoding sPLA₂-IIA (page 284, column 2). Not inconsistently, Murakami et al. (*supra*) suggests that type IIA and type V

enzymes are functionally redundant and act in concert with cytosolic PLA2; see entire document (e.g., the abstract).

So will the blockade of the catalytic activity of human sPLA₂-IIA by the disclosed cyclic peptide designated "c(2Nap)LS(2Nap)R", for example, be sufficient to achieve therapeutic effect in treating prostate cancer, in general, in humans, or might the its lack of expression by DU-145 cells and/or the compensation of its loss of expression and/or activity by other PLA2 isoenzymes point to its non-essential nature in tumorigenesis and the progression of the disease?

It is not without additional studies that it will be known, and given the complexity and duration of such studies, for example, it is evident that the claimed invention is not reasonably enabled for use without undue and/or unreasonable experimentation

As a last point, with particular regard to claim 6-9, there is at least an implication in this application that the cyclization of a peptide capable of inhibiting an enzyme will make a more potent inhibitor⁶; however, there is evidence that the effects of cyclization or the induction of other conformation constraints upon the activity of a peptide inhibitor cannot be predicted, which suggests potentiation of inhibitory effects by an induction of conformation constraint cannot be expected.

In support of this position, Thwin et al. (*J. Med. Chem.* 2007; **50**: 5938-5950) (of record) describes their surprising finding that cyclization of a peptide that inhibits a sPLA₂ enzyme abolished the activity of the peptide, despite the fact that Church et al. (*J. Biol. Chem.* 2001 Aug 31; **276** (35): 33156-33164) (of record) demonstrated that cyclic peptides showed increased potency, as compared to their linear counterparts; see entire document (e.g., page 5943, column 2).

Claims 6-8 are directed to molecules or derivatives thereof that need not have any particular structure, but which function as a selective inhibitor of any of a plurality of "sPLA₂-IIA" enzymes. The breadth of the claims is particularly evident in light of the definition of the term "derivative"; see, e.g., paragraph [0085] of the published application. According to this definition, the inhibitor might be a non-naturally occurring

⁶ See, e.g., paragraph [0143] of the published application, which cites Church et al.

a-amino acid, which is an analogue of any of the amino acid residues at positions 70 to 74 of the amino acid sequence of human "sPLA₂-IIA" protein. While it is not reasonably expected that a non-naturally occurring amino acid will be found to inhibit a "PLA₂" enzyme, it is apparent that the amount of guidance, direction and exemplification provided in this application is not reasonably commensurate with the breadth of the claims, and would not enable the skilled artisan to make and then use such different inhibitors in practicing the claimed invention to achieve the claimed objective without undue and/or unreasonable experimentation.

As for claim 9, although the scope of the claim is considerably more limited, since the molecule that is an inhibitor must have a primary structure that is recited in the claim, it still encompasses the use of analogues of the peptide first disclosed by Tseng et al. (*surpa*), which have not been shown to be effective to inhibit an activity of any a "PLA₂" enzyme, including a human "sPLA₂-IIA" enzyme. As evident from the disclosure of Thwin et al. (*supra*), the skilled artisan cannot always correctly predict the effect of derivatizing or making substitutions in the amino acid sequence of a peptide upon the activity of the peptide.

Consistent with this position, it is noted that Church et al. (*supra*) describes analogues of the peptide first disclosed by Tseng et al. (*surpa*), which lack the inhibitory activity of original peptide; see entire document (e.g., page 33158, Figure 1). In particular, Church et al. discloses that two peptides (i.e., "ALSYK" and "FLSYE" were inactive; and although active, two other peptides (i.e., "FLTYK" and "FWSYK") were considerably less inhibitory than the original peptide used as a positive control (i.e., "FLSYK") (page 33158, Figure 1).

The specification discloses, because of the inherent flexibility of the linear peptide sequence, inhibition by the original peptide described by Tseng et al. (*supra*) was weak, so Applicant began developing analogues of this peptide with the aim of developing a more potent inhibitor that might be useful in treating prostate cancer; see, e.g., paragraph [0143] of the published application.

Such disclosure implies that analogues of the original peptide described by Tseng et al. (*supra*), which are less inhibitory than even the original peptide, are not suitable for use in practicing the claimed invention.

Tseng et al. (*supra*) also describes two analogues of the originally described peptide inhibitor, including "KFLSY" and "LSYKF", but "LSYKF" and other analogues were found to be wholly ineffective and "KFLSY" retained only a fraction of the inhibitory activity of "FLSYK"; see entire document (e.g., page 23997, Table III).

Church et al. (*supra*) describe a number of other analogues, but apart from the disclosed cyclic peptide and its cyclic analogues (i.e., "cFLSYK", "cFLSYR" and "c(2Nap)LS(2Nap)R") most were inactive or were only marginally more effective in the assays than the linear peptide (i.e., "FLSYK"); see, e.g., page 33159, Table I; and page 33161, column 2). Church et al. discloses that "cFLSYR" was 5-fold more effective in the assay, as compared to the originally described linear peptide, without disclosing or showing what improvement was achieved by the cyclization of the linear peptide to produce "cFLSYK" (page 33161, column 2). So, since as discussed above, Sved et al. discloses that only "c(2Nap)LS(2Nap)R" was effective *in vivo* at a dose of 1 mg/mg to slow the growth of PC-3 tumors in mice, whereas "cFLSYR" was not, it is reasonable to question whether "cFLSYK" could be used to achieve the claimed therapeutic effect in treating prostate cancer in a subject, particularly since Church et al. (*supra*) discloses that the peptides were toxic to cultured human cells at concentrations beginning at about 100 μ M. As such, though the peptides may be effective inhibitors at certain doses, those doses may be too toxic to the subject to justify treatment; and perhaps only after additional studies are performed to assess the effectiveness of each of the different peptides encompassed by the claims will it be known whether the claimed invention (or which embodiments thereof) can be used efficaciously to treat prostate cancer, in general, in subjects, particularly where those subjects are human patients.

In conclusion, though Applicant's arguments have been carefully considered, upon equally careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), it has been determined

that the amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not have been sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

16. The rejection of claims 1-3 and 6-10 under 35 U.S.C. 102(a), as being anticipated by Sved et al. (*Cancer Res.* 2004 Oct 1; **64**: 6934-6940) (of record), is maintained.

At page 19 of the amendment filed January 16, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 1-3 and 6-10 do not properly benefit under §§ 119 and/or 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

To receive benefit of the earlier filing date under §§ 119 and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). See M.P.E.P. § 201.11.

Accordingly, the effective filing date of claims 1-3 and 6-10 is deemed the filing date of the instant application, namely January 14, 2005.

Sved et al. teaches the inhibition or reduction of the proliferation rate of LNCaP and PC-3 prostate cancer cells *in vitro* by contacting the cells with an inhibitor of the catalytic phospholipase A₂ activity of the sPLA₂-IIA enzyme expressed by those cells; see entire document (e.g., the abstract). In particular, Sved et al. teaches cyclic peptides designated "cFLSYR" and "c(2Nap)LS(2Nap)R" are effective inhibitors, which slowed the rate of growth of established PC-3 tumors in nude xenograft mice that received doses of either 1 or 10 mg/kg three times a week once the tumor had reached the size of 5 x 5 mm; see, e.g., page 6939, column 1.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. The rejection of claims 1-3 under 35 U.S.C. 103(a), as being unpatentable over Graff et al. (*Clin. Cancer Res.* 2001 Dec; **7**: 3857-3861) (of record; cited by Applicant) in view of Attiga et al. (*Cancer Res.* 2000 Aug 15; **60**: 46-29-4637) (of record; cited by Applicant), Liu et al. (*J. Urol.* 2000 Sep; **164**: 820-825) (of record), or Kelavkar et al. (*Carcinogenesis.* 2001 Nov; **22** (11): 1765-1773) (of record), is maintained.

At page 19 of the amendment filed January 16, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the preceding Office action, Graff et al. teaches the expression of the gene encoding human sPLA₂-IIA is specifically increased with progression of human prostate cancer cells to androgen independence; see entire document (e.g., the

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abstract). Graff et al. teaches the expression of sPLA₂-IIa is inversely related to patient survival; see, e.g., the abstract. Accordingly, Graff et al. teaches their report "provides compelling evidence that enhanced sPLA₂-IIa expression may be involved in the malignant progression of human prostate cancer and suggests that specific inhibitors of the group IIa sPLA₂ may be useful for prostate cancer chemotherapy" (page 3860, column 2).

Accordingly, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with an agent that inhibits the expression and/or activity of human sPLA₂-IIa in prostate cancer cells. One ordinarily skilled in the art at the time the invention was made would have been motivated to do so in order to treat prostate cancer.

One ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully doing so in light of the disclosure of Attiga et al., Liu et al., or Kelavkar et al.

Attiga et al. teaches eicosanoids modulate the interaction of tumor cells with various host components in cancer metastasis, and their synthesis involves the release of arachidonic acid from cellular phospholipids by phospholipase A₂, followed by metabolism by cyclooxygenases and lipoxygenases; see entire document (e.g., the abstract). Attiga et al. teaches the invasion of prostate cancer cells (i.e., PC-3 and DU-145 cells) is inhibited by a PLA₂ inhibitor, a general cyclooxygenase inhibitor, and a selected COX-2 inhibitor; see, e.g., the abstract. Attiga et al. teaches treatment of the cells with these inhibitors reduced their secretion of matrix metalloproteinases; see, e.g., the abstract.

Liu et al. teaches the growth of PC-3 xenograft tumors in nude mice was inhibited by a COX-2 inhibitor; see entire document (e.g., the abstract). Liu et al. teaches COX-2 inhibition is even more effective *in vivo* than might be predicted because treatment of prostate cancer cells with the inhibitor induces the cells to undergo apoptosis and causes down-regulation of the gene encoding VEGF, so as to have anti-angiogenic effects; see, e.g., page 820, column 2.

Kelavkar et al. teaches the gene encoding 15-lipoxygenase-1 is overexpressed in PC-3 prostate cancer cells, and that aberrant expression of enzymes that convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites appears to significantly contribute to the development of prostate cancer; see entire document (e.g., the abstract; and page 1765, column 2). Kelavkar et al. teaches that overexpression of 15-lipoxygenase-1 by PC-3 cells leads to the up-regulation of the gene encoding VEGF; see, e.g., page 1771, column 2. Kelavkar et al. teaches that the proliferation of PC-3 cells is inhibited by treating the cells with an inhibitor of 15-lipoxygenase-1; see, e.g., the abstract.

Thus, in view of the disclosures of Attiga et al., Liu et al., or Kelavkar et al., one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully practicing the claimed invention because PLA₂ (e.g., sPLA₂-IIA) acts upstream of the cyclooxygenases and lipoxygenases, which in turn act to convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites that contribute to the development of prostate cancer. Because inhibition of the cyclooxygenases and lipoxygenases has proven effective to inhibit the proliferation of prostate cancer cells, as well as the spread of the cancer by anti-angiogenic mechanisms, the artisan would reasonably expect that the inhibition of sPLA₂-IIA in prostate cancer cells will result in the inhibition of their proliferation by inhibiting the activities of the cyclooxygenases and lipoxygenases acting downstream of PLA₂ in the pathway leading to the production of the eicosanoids, such as prostaglandins and leukotrienes, as well as in the regulation of the gene encoding VEGF.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant has argued that Graff et al. does not teach the structure of a selective inhibitor of sPLA₂-IIA.

In response, the claims are not directed to an inhibitor having any particular structure.

Applicant has argued that Graff et al. does not teach or suggest the use of the particular inhibitors that are described in this application.

In response to Applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the particular structure of an inhibitor) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant has argued that Attiga et al. teaches an inhibit that is not a selective inhibitor.

In response, the term "selective" is not defined in the specification. It is apparent however that the term "selective" does not mean "exclusive". Moreover, the claims do not make evident how selective an agent must be; and it cannot be ascertained from the disclosure whether an agent that inhibits certain types of enzymes, but not other types of enzymes, is or is not suitable for use as a "selective" inhibitor of the sPLA₂-IIA enzyme.

Applicant has argued that the disclosure of Liu et al. is irrelevant; the Examiner disagrees. The significance of the publication has been explained in the rejection.

In further response, as explained in the preceding rejections of the claims under 35 U.S.C. § 112, first paragraph, the activity of the sPLA₂-IIA that must be inhibited by the inhibitor, such that inhibition or reduction of proliferation of prostate cancer cells is achieved, or such that the disease is "treated" has not been described; and again the inhibitor need not have any particular structure, since it is only described by the effect that must be achieved when it is administered to prostate cancer cells or to a subject diagnosed with the disease. Liu et al. teaches the growth of PC-3 xenograft tumors in nude mice was inhibited by the COX-2 inhibitor. Thus, the inhibitor described by Liu et al. is functionally identical to the inhibitor to which the claims are directed.

Additionally, though Applicant has argued that COX-2 "lies downstream of sPLA₂-IIA", it is not evident to which physiological or biochemical pathway Applicant refers; and besides, there is no requirement that the inhibitor to which the claims are directed act directly upon the sPLA₂-IIA. It seems that an inhibitor might just as effectively act indirectly to selectively inhibit an activity of sPLA₂-IIA, particularly if the inhibitor is an inhibitor of COX-2 and COX-2 is a element of the same physiological or biochemical pathway.

Applicant has argued that a skilled addressee could not predict that inhibiting sPLA₂-IIA would produce a similar effect as COX-2 inhibition.

In response, it is not understood why Applicant would submit that a skilled addressee should be able to predict that inhibiting sPLA₂-IIA would produce a similar effect as COX-2 inhibition. The claims are drawn to a method of inhibiting or reducing the proliferation of prostate cancer cells or of treating prostate cancer by administering to the cells or the subject diagnosed with the disease a substance that is capable of achieving that effect. Graff et al. provides evidence that enhanced sPLA₂-IIa expression may be involved in the malignant progression of human prostate cancer and suggests that specific inhibitors of sPLA₂-IIA may be useful for prostate cancer chemotherapy; and Liu et al. teaches the growth of PC-3 xenograft tumors in nude mice was inhibited by a COX-2 inhibitor. Accordingly, one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully practicing the claimed invention because sPLA₂-IIA acts upstream of the cyclooxygenases and lipoxygenases, which in turn act to convert unsaturated fatty acid arachidonic acid and linoleic acid to bioactive lipid metabolites that contribute to the development of prostate cancer. Because inhibition of the cyclooxygenases and lipoxygenases has proven effective to inhibit the proliferation of prostate cancer cells, as well as the spread of the cancer by anti-angiogenic mechanisms, the artisan would reasonably expect that the inhibition of sPLA₂-IIA in prostate cancer cells will result in the inhibition of their proliferation by inhibiting the activities of the cyclooxygenases and lipoxygenases acting downstream of PLA₂ in the pathway leading to the production of

the eicosanoids, such as prostaglandins and leukotrienes, as well as in the regulation of the gene encoding VEGF.

Applicant has not dissimilarly argued that the disclosure of Kelavkar et al. also fail to remedy the deficiency of the Graff et al.; but again the claims are not drawn to an inhibitor having any particular structure or which act directly upon sPLA₂-IIA. The limitations of the claims are met by the teachings and suggestions of Graff et al. it is view of the teachings and suggestions of the secondary references that it is submitted that the artisan of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in practicing the claimed inventions to achieve the claimed objectives.

Accordingly, although Applicant's arguments have been carefully considered, the claimed process would have been obvious given the teachings and suggestions of Graff et al.; and in light of the secondary references, the artisan of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in practicing the claimed inventions to achieve the claimed objectives.

19. The rejection of claims 6-10 under 35 U.S.C. 103(a), as being unpatentable over Graff et al. (*Clin. Cancer Res.* 2001 Dec; **7**: 3857-3861) (of record; cited by Applicant) in view of Attiga et al. (*Cancer Res.* 2000 Aug 15; **60**: 46-29-4637) (of record; cited by Applicant), Liu et al. (*J. Urol.* 2000 Sep; **164**: 820-825) (of record), or Kelavkar et al. (*Carcinogenesis.* 2001 Nov; **22** (11): 1765-1773) (of record), as applied to claims 1-3 above, and further in view of Church et al. (*J. Biol. Chem.* 2001 Aug 31; **276** (35): 33156-33164) (of record), is maintained.

At page 22 of the amendment filed January 16, 2009, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

As explained in the preceding Office action, Graff et al. teaches that which is set forth in the above rejection of claims 1-3 under 35 U.S.C. § 103(a), but does not expressly teach or suggest that the sPLA₂-IIA inhibitor is a cyclic peptide or analogue

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derived from the linear peptide first described by Tseng et al. (*supra*), which is a peptide consisting of the amino acid residues at positions 70-74 of a purified human sPLA₂-IIA protein.

As further explained in the preceding Office action, Church et al. describes the identification of a peptide consisting of the amino acid residues at positions 70-74 of a purified human sPLA₂-IIA protein, which is capable of inhibiting the catalytic activity of sPLA₂-IIA; see entire document (e.g., the abstract). Church et al. teaches this peptide, first described by Tseng et al. (*supra*), consists of the amino acid sequence: F-L-S-Y-K; see, e.g., the abstract. Church et al. teaches cyclization of the peptide or of an analogue (i.e., F-L-S-Y-R) increased the inhibitory potency of the peptide, as compared to the original peptide; see, e.g., page 33161, column 2. However, Church et al. further discloses that a cyclic analogue of the peptide in which the phenylalanine and tyrosine residues are replaced by 2-naphthylalanine is even more potent; see, e.g., page 33161, column 2. Church et al. designates this cyclic analogue: "c(2NapA)LS(2NapA)R"; see, e.g., page 33162, Table II.

Accordingly, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with the cyclic peptides described by Church et al., which were demonstrated to be highly potent inhibitors of sPLA₂-IIA, such as the peptide designated by Church et al. as "c(2NapA)LS(2NapA)R". One ordinarily skilled in the art at the time the invention was made would have been motivated to do so in order to treat prostate cancer.

Again, one ordinarily skilled in the art at the time the invention was made would have had a reasonable expectation of successfully doing so in light of the disclosure of Attiga et al., Liu et al., or Kelavkar et al.

Applicant has argued that Church et al. teaches away from the claimed invention; the Examiner disagrees. Church et al. teaches a selective inhibitor of human sPLA₂-IIA. Given Graff et al., it would have been obvious to one ordinarily skilled in the art at the time the invention was made to have inhibited the growth or proliferation of prostate cancer cells by contacting the cells with the cyclic peptides described by Church et al.

Accordingly, although Applicant's arguments have been carefully considered, the claimed process would have been obvious given the teachings and suggestions of Graff et al.; and in light of the secondary references, the artisan of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in practicing the claimed inventions to achieve the claimed objectives.

Conclusion

20. No claim is allowed.

21. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/

Primary Examiner, Art Unit 1643

slr

April 13, 2009